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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,594	06/22/2001	Vassilios Papadopoulos		6687

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,594	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16,41,43,44,46-52,57-64 and 69-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10-16,41 and 48-52* is/are allowed.

6)☒ Claim(s) *43-44, 46-47, 57-64, 69-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 25 March 2004 under 37 CFR 1.114 based on parent Application No. 09/762,594 is acceptable and an RCE has been established. An action on the RCE follows.

Status of Application, Amendments and/or Claims

The amendment of 25 March 2004 has been entered in full. Claims 43-44, 46-47, 50-5260, 64, 72, and 76 are amended. Claims 1-9, 17-40, 42, 45, 53-56, and 65-68 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 10-16, 41, 43-44, 46-52, 57-64, and 69-76 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the declaration set forth at pg 3 of the previous Office Action (25 September 2003) is *withdrawn* in view of the new declaration submitted on 02 January 2004.

2. The objection to claim 51 as set forth at pg 3 of the previous Office Action (25 September 2003) is *withdrawn* in view of the amended claim (25 March 2004).

3. The rejection of claims 50-52 under 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 7-8 of the previous Office Action (25 September 2003) is *withdrawn* in view of the amended claims (25 March 2004).

4. The rejection of claims 42-47 and 53-76 under 35 U.S.C. § 112, first paragraph (scope of enablement) as set forth at pg 3-7 of the previous Office Action (25 September 2003) is

withdrawn in view of the cancelled claims and Li et al. (Molec Endocrinol 15(12): 2211-2228, 2001). Please see section on 35 U.S.C. § 112, first paragraph, below.

5. The rejection of claims 45-47 and 65-76 under 35 U.S.C. § 112, second paragraph as set forth at pg 11 of the previous Office Action (25 September 2003) is *withdrawn* in view of the amended and cancelled claims (25 March 2004).

Claim Rejections - 35 USC § 112, first paragraph

Upon further consideration of the claims, the specification, and Li et al. (Molec Endocrinol 15(12): 2211-2228, 2001; a post-filing date reference by the instant inventors), the Examiner has rejected the claims listed below under total lack of enablement rather than scope of enablement.

6. Claims 43-44, 46-47, 57-64, 69-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to an isolated nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 and encodes a polypeptide that is capable of regulating progesterone synthesis. The claims recited an isolated nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 and encodes a polypeptide that impairs cholesterol delivery. The claims recite a process of producing a peripheral-type benzodiazepine-associated protein. The claims recite a vector comprising a heterologous promoter linked the PAP7 nucleotide sequence and reagents comprising the nucleic acid.

The specification of the instant application teaches that the PAP7 partial sequence including the PBR binding domain is subcloned into a pSVzeo mammalian expression vector. This pSVzeoPAP7 vector is transiently transfected into MA-10 cells and the capability of steroid biosynthesis of both empty vector pSVzeo transfectants and pSVzeoPAP7 transfectants is checked by monitoring the progesterone production in response to hormonal (hCG) stimulation (pg 47, lines 14-23). The specification discloses that *partial PAP7* transfectants significantly *reduce* the level of progesterone production in MA-10 cells as compared with pSVzeo vector transfectants at a dose and time dependent manner (pg 47, lines 23-26; Fig 6). However, Li et al. teach that MA-10 cells transfected with *full-length PAP7* show an *increased* ability to form progesterone in response to hCG (pg 2219, col 1, 2nd full ¶; Figure 9A). Similarly, Li et al. disclose that transfection of MA-10 cells with full-length PAP7 followed by treatment with hCG results in higher production of pregnenolone, reflecting increased accumulation of cholesterol at the inner mitochondrial membranes (pg 2219, col 2, 1st full ¶). Li et al. also teach that transfection of MA-10 cells with the partial PAP7 sequence inhibit pregnenolone formation by 70% (pg 2219, 1st full ¶; Fig 10). Therefore, the full-length PAP7 protein and the partial PAP7 protein have opposite functions regarding progesterone production and pregnenolone formation (cholesterol accumulation). Undue experimentation would be required by one skilled in the art to generate an isolated nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of SEQ ID NO: 2 and encodes a polypeptide that is capable of regulating progesterone biosynthesis or impairs cholesterol delivery. The skilled artisan must also resort to trial and error experimentation to screen all possible derivatives for such activities. Such trial and error is considered undue. Although amino acids 228-445 of SEQ ID NO: 7 are required for a decrease

in progesterone production as evidenced by Li et al., undue experimentation would be required of the skilled artisan to determine which amino acids impart the function of full length PAP7 (e.g., increased progesterone biosynthesis). There is little or no guidance in the specification indicating which amino acids are required for the biological activity of full-length PAP7 or a protein encoded by an isolated nucleic acid sequence that is 90% identical to SEQ ID NO: 2. There is also no guidance in the instant specification as to the specific amino acid sequence that comprises the partial PAP7 protein. Additionally, a large quantity of experimentation would be required by one skilled in the art to generate and screen for nucleic acid molecules that encode a polypeptide that impairs cholesterol delivery or regulates progesterone biosynthesis and hybridizes to the complement of the nucleic acid of SEQ ID NO: 2.

Furthermore, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions.

As discussed in the previous Office Action of 25 September 2003, relevant literature reports examples of growth factor polypeptide mutations which alter the normal activity of the polypeptide. For example, Wuyts et al. (J Immunol 163: 6155-6163, 1999) establishes that NH_2- and COOH- terminal truncations of granulocyte chemotactic protein-2 (GCP-2) have enhanced neutrophil chemotactic potency as compared to wild-type GCP-2 (abstract; pg 6157-6158). Sher

et al. (J Biol Chem 274(49):35016-35022, 1999) disclose that keratinocyte growth factor (FGF-7) acts predominantly on cells of epithelial origin and regulates processes in embryonal and adult development, including cell growth, differentiation, cell migration, and repair of epithelial tissues (pg 35016, ¶ 1). Sher et al. demonstrate that point mutations in a loop of FGF-7 do not alter receptor binding affinity, but cause reduced mitogenic potency and reduced ability to induce receptor-mediated phosphorylation events (pg 35020-35021). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, the specification fails to teach the skilled artisan how to make and use biologically active PAP7 variants without resorting to undue experimentation to determine what the specific biological activities of the variants are.

Applicant asserts in the response of 25 March 2004 that the specification fully enables one of skill in the art to identify PAP7 variants or hybridizing nucleic acids having the biological activity of impairing cholesterol delivery. Applicant contends that the specification discloses that PBR binds PAP7 and that cholesterol transport into a cell is impaired (pg 8). Applicant argues that these methods allow for the identification of fragments that can be used as antagonists to inhibit the PAP7-PBR association and reduce or inhibit PBR activity and modulate cholesterol transport (pg 34-35). Applicant indicates that the PAP7 fragment of the instant specification also inhibited pregnenolone formation in the inner mitochondrial membrane of MA-10 cells. Applicant states that inhibition of pregnenolone formation is due to a decrease in accumulation of cholesterol at the IMM and reflects PAP7's ability to impair cholesterol

transport. Applicant's arguments have been fully considered but are not found to be persuasive. The specification does not teach any methods or working examples that indicate full length PAP7 or any PAP7 fragments are able to mediate cholesterol delivery. Also, the specification does not teach any methods or working examples that monitor pregnenolone formation by full-length PAP7 or partial PAP7, as shown in Li et al. There is no nexus in the instant specification that pregnenolone reflects accumulation of cholesterol at the inner mitochondrial membrane (IMM). There are no methods or working examples in the specification that indicate PAP7 regulates PBR activity in cholesterol transport.

Furthermore, the broad brush discussion of making and screening for PAP7 variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the full length nucleic acid sequence of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 7 are disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error.

The Examiner acknowledges that it is not a function of the claims to specifically exclude possible inoperative embodiments, and the presence of inoperative embodiments within the scope of a claim does not preclude enablement of the claim. However, the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. MPEP § 2164.08(b) states that "claims reading on significant numbers of inoperative embodiments would render the claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which recite broad structural and functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 43-44, 46-47, 57-64, 69-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 9-11 of the previous Office Action of 25 September 2003 and at pg 9-12 of the Office Action of 10 April 2003.

The claims are directed to an isolated nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 and encodes a polypeptide that is capable of regulating progesterone synthesis. The claims recited an isolated nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 and encodes a polypeptide that impairs cholesterol delivery. The claims recite a process of producing a peripheral-type benzodiazepine-associated protein. The claims recite a vector

comprising a heterologous promoter linked the PAP7 nucleotide sequence and reagents comprising the nucleic acid.

Applicant's arguments (25 March 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the claimed variants and hybridizing nucleic acids that encode a polypeptide capable of regulating progesterone biosynthesis are described in the specification. Applicant submits that the specific biological activities of interacting with PBR and mediating cholesterol delivery are described in the specification and are to be correlated with the claimed variant and hybridizing nucleic acids (pg 34, lines 14-15; pg 49, lines 30-35; pg 50, lines 12-17; pg 19, lines 19-21). Applicant states that, for example, the specification teaches that due to the progesterone studies in Example 5, it is believed that PAP7 binds to PBR and a fragment of PAP7 would act as a competitor of the native PAP7 (pg 51). Applicant argues that the biological activity of mediating cholesterol delivery is discussed throughout the specification (pg 2; pg 35, lines 25-36; pg 36, line 10; pg 49; pg 51, lines 27 through pg 52, lines 5). Applicant asserts that the specification not only describes the specific PAP biological activities of progesterone regulation, cholesterol transport mediation, and PBR binding, but also demonstrate these specific activities wither directly in the specification (Examples 1 and 5) or in Li et al. Applicant concludes that the instant specification is analogous to Example 14 of the Revised Interim Written Description Guidelines since the specific activity of PBR binding and cholesterol transport mediation is sufficiently disclosed in the application.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Applicant has not provided evidence to demonstrate that the skilled artisan would

be able to envision the detailed structure of the infinite number of polynucleotides recited in the claims. The description of one full length PAP7 polynucleotide and polypeptide in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and variants with at least 90% or more sequence identity to the polypeptide of SEQ ID NO: 7 that impair cholesterol delivery or regulate progesterone biosynthesis. Furthermore, the broad brush discussion of making or screening for variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

Furthermore, as discussed in the previous Office Action, the fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the protein and variants have a specific activity disclosed in the specification. However, regarding the PAP7 polynucleotides and polypeptides of the instant invention, the specification does not teach any significance or functional characteristics of all possible PAP7 polynucleotide sequences that are 90% identical to the sequence of the nucleic acid sequence of SEQ ID NO: 2 or to the nucleotide sequence that encodes the polypeptide set forth in SEQ ID NO: 7. One skilled in the art would not be able to recognize a variant of PAP7 because the full-length PAP7 and the partial PAP7 have opposite functions regarding progesterone production and pregnenolone formation (cholesterol accumulation), as evidenced by the instant specification and Li et al. There is little or no

guidance in the specification indicating which amino acids are required for the biological activity of full-length PAP7 or a protein encoded by an isolated nucleic acid sequence that is 90% identical to SEQ ID NO: 2.

Additionally, the recitation of hybridization conditions in the claims does not yield adequate written description of the polynucleotides encompassed. The claims encompasses an infinite number of polynucleotides that hybridize to the nucleic acid sequence of SEQ ID NO: 2 and that impair cholesterol delivery or regulate progesterone biosynthesis. These polynucleotides may be structurally and functionally divergent from the polynucleotide of SEQ ID NO: 2.

8. Claims 44, 47, 61-64, and 73-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 44 is directed to an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that impairs cholesterol delivery. Claim 47 recites an isolated nucleic acid that encodes a polypeptide that impairs cholesterol delivery and hybridizes to the complement of the nucleic acid of claim 41(a) or 41(b). The claims also recite vectors comprising the nucleic acids, host cells comprising the vectors, a process of producing a PAP, and diagnostic agents comprising the nucleic acids.

The specification as originally filed does not provide adequate written description for an isolated nucleic acid that encodes a polypeptide that *impairs* cholesterol delivery. It is not expressly asserted, nor does it flow naturally from the specification. Although the Examiner indicated in the Advisory Action of 15 March 2004 that support for the phrase "impairing cholesterol delivery/transport" could be located at the top of pg 4 of the specification, this phrase was not associated with the claimed invention. This phrase was being used to describe the cholesterol transport mechanisms in PBR.

Conclusion

Claims 10-16, 41, and 48-52 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
17 June 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER